Remarks

Claims 1-8, 13-17, 20-25, 57, 60-70, and 77-81 are pending. Claims 2-4, 7, 8, 61, 65, and 67 are withdrawn from consideration. Claims 1 and 5 are amended herein. Claim 1 is amended to incorporate the limitations of canceled claim 62. Claim 5 is amended to incorporate the limitations of canceled claim 68. Support for additional amendments of claims 1 and 5 can be found in the specification at page 2, lines 6-14, page 3, lines 3-6, page 11, lines 5-28, page 12, lines 26-39 and page 38, lines 23-32.

Claims 62 and 68 are canceled herein. Claims 9, 12, 18-19, 25-56, 58-59 and 71-76 were canceled previously. Following entry of this amendment, claims 1, 5, 6, 13-17, 20-25, 57, 60, 63-64, 66, 69-70, 77-81 are pending.

No new matter is added herein. Reconsideration of the subject application is respectfully requested.

Telephone interview

Applicants thank Examiners Yu and Helms for the helpful telephone conference on February 24, 2004, with Applicant's representatives, Susan Alpert Siegel, Ph.D. and Anne Carlson, Ph.D, wherein the Office action was discussed. Two abstracts, documenting a relationship between angiogenesis and periodontal disease, were forwarded to the U.S. Patent and Trademark Office for their consideration. For the Examiners' convenience, additional copies of these abstracts are attached hereto as Exhibits A and B. In addition, amendment of the independent claims was discussed.

Election/Restriction

The Office action states that the claims drawn to methods of inhibiting endothelial cell growth and inhibiting angiogenesis are pending. Thus, it is the Applicants' understanding that the Examiner has rejoined the subject matter of Groups I and II. Claims 2-4, 7-8, 61, 65 and 67 have been withdrawn from consideration, as being directed to a non-elected invention. It is the also the Applicants' understanding that the restriction requirement has been made final.

Information Disclosure Statement

The Office action states that "the list of the Information Disclosure Statement" submitted on April 5, 2001 is missing from the file. Thus, it is the Applicants understanding that the PTO-1449 form has been misplaced. A copy of the PTO-1449 form submitted on April 5, 2001 is attached (Exhibit C).

Attached is a copy of the return post card documenting receipt by the United States Patent and Trademark Office (PTO) of the Information Disclosure Statement, the PTO-1449, and the cited references on April 5, 2001 (Exhibit D). Thus, it is the Applicants' understanding that no additional fee is due.

If the copies of the references are also missing from the U.S. PTO's file, then the Applicants respectfully request that the Examiner contact the undersigned by telephone, and additional copies of the references will be provided. If the references have already been received, or are otherwise available to the Examiner, Applicants respectfully request that the Examiner initial and date the attached PTO-1449 form to indicate that the references have been considered, and return a copy of the signed form to the Applicants' representative at the address listed below.

Rejections Under 35 U.S.C. §112, first paragraph

Claims 1, 5, 6, 13-17, 20-25, 57, 60, 62-64, 66, 68-70, 77-81 are rejected under 35 U.S.C. §112, first paragraph, as allegedly a genus of polypeptides that are defined only by sequence identity (90-98%) or as a fragment are not described in the specification. Claims 62 and 68 are canceled herein, rendering the rejection moot as applied to these claims. Applicants respectfully disagree with the rejection as applied to claims 1, 5, 6, 13-17, 20-25, 57, 60, 63-64, 66, 69-70, 77-81.

The specification clearly describes polypeptides with at least 95% identity to calreticulin (SEQ ID NO: 2). For example, these polypeptides are disclosed in the specification on page 12, line 8 to page 13, line 3. Specific computer programs are also disclosed that can be used for a comparison of sequence identity (see the specification on page 12, lines 20-25). In addition, a specific sequence of a polypeptide (SEQ ID NO: 3) with a 95% sequence identity to calreticulin is provided. This polypeptide inhibits endothelial cell growth (see the specification on page 32). Furthermore, the specification discloses that the first 120 amino acids are not essential for

inhibiting endothelial cell growth (see the specification on page 11, lines 9-13, page 20, lines 25-30), indicating that these amino acids could be varied.

With regard to fragments of SEQ ID NO: 2 that inhibit endothelial cell growth or angiogenesis, the specification provides adequate written description for such fragments. Specifically, therapeutically effective fragments are described in the specification on page 11, lines 5-30. Moreover, the sequence of several active fragments (for example, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 8) are disclosed. Indeed, the specification indicates that an amino acid sequence found between amino acids 132-180 of SEQ ID NO: 2 (also shown as SEQ ID NO: 6) is included in these fragments (see the specification at page 20, lines 10-25). As noted above, the specification discloses that the first 120 amino acids are not essential for endothelial cell growth (see the specification on page 11, lines 9-13, page 20, lines 25-30).

In order to clarify that the claimed polypeptides must be therapeutically effective, claim 1 has been amended to recite that the polypeptide "inhibits endothelial cell growth" and claim 5 has been amended to recite that the polypeptide "inhibits angiogenesis." Applicants note that assays for testing these activities are described in the specification on page 34, lines 30-38. Moreover, results from such testing of a polypeptide (SEQ ID NO: 3) having an amino acid sequence 95% identical to SEQ ID NO: 2, and results from testing of effective fragments of SEQ ID NO: 2 (SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 8) are presented in the Examples section (see the specification on page 23, line 34 to page 25, Table 4 (angiogenesis), and on page 18, line 12 to page 22, Table 3 (endothelial cell growth).

Thus, Applicants submit that there is clearly sufficient descriptive support in the specification for polypeptides of at least 95% sequence identity to SEQ ID NO: 2, and therapeutically effective fragments thereof, that inhibit endothelial cell growth and/or inhibit angiogenesis. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 20 was rejected as allegedly not being enabled by the specification. The Office action asserts that the specification does not teach any relationship between angiogenesis and periodontal disease. Thus the Office action alleges that the specification is not enabling for claims directed to the use of a polypeptide with at least 95% sequence identity to SEQ ID NO: 2,

or a therapeutically effective fragment thereof, to treat periodontal disease. Applicants respectfully disagree with this rejection.

Applicants note that the specification at page 39, lines 11-13 teaches that angiogenesis is associated with periodontal disease. Moreover, Polverini *et al.* (*Crit. Rev. Oral Biol. Med.*, 6:230-247, 1995; Exhibit A) and Zoellner *et al.* (*J. Oral Pathol. Med.*, 18:333-338, 1989; Exhibit B) are two examples from the prior art that demonstrate it was known to those of skill in the art at the time the application was filed that a relationship existed between angiogenesis and periodontal disease.[1]

Legal precedent holds that the specification need not disclose what is well known in the art (Lindemann Maschinenfabrik GmbH V. American Hoist & Derrick Co., 221 USPQ 481, 489 (Fed. Cir. 1984)). As the relationship between periodontal disease and angiogenesis was well known in the art at the time the application was filed, the mechanistic details of the relationship between angiogenesis and periodontal disease need not be fully described in the specification. Moreover, Applicants submit that a complete understanding of the mechanistic relationship between angiogenesis and periodontal disease is not necessary for one of skill in the art to practice the claimed methods. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §102

Claims 1, 5, 6, 57, 60, 62-64, 66, 68-70, and 78 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,426,097 (hereinafter the '097 patent; issued June 20, 1995). Claims 62 and 68 are canceled herein rendering the rejection moot as applied to these claims. Applicants respectfully disagree with this rejection as applied to claims 1, 5-6, 57, 60, 63-64, 66, 69-70 and 78, as amended.

The '097 patent teaches that calreticulin can be used to block or prevent thrombosis (blood clotting) in a subject in need of treatment with such an agent without causing a defect in hemostasis (the arrest of bleeding). A method for enhancing the action of other antithrombotic agents is further provided. These methods include intracoronary or intravenous administration of

[1] Copies of these references were faxed to the U.S. PTO on February 24, 2004. However, for the Examiner's convenience, additional copies are enclosed.

calreticulin at a dose of 0.04 mg/kg to 0.4 mg/kg (see the '097 patent at column 4 to column 5) into a subject to block or prevent the formation of a blood clot.

The Office action suggested that methods of inhibiting endothelial cell growth or angiogenesis in subjects are inherent to the methods disclosed in the '097 patent. Applicants respectfully disagree with this assertion.

Anticipation requires that each and every element of the claimed invention must be present in the prior art either explicitly or inherently (See Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc., 246 F.3d 1368, 1374 (Fed. Cir. 2001); Mehl/Biophile Int'l Corp. v. Milgraum, 192 F.3d 1362, 1365, 52 USPQ2d 1303 (Fed. Cir. 1999). Thus, if a claimed process is not disclosed in a single prior art reference, arguments of inherency are immaterial.

The '097 patent discloses that calreticulin can be administered to prevent blood clotting in a subject in need of antithrombotic therapy. Angiogenesis involves the development of new blood vessels (see Exhibit E), whereas thrombosis involves the development of clots within blood vessels (see Exhibit F). Since angiogenesis and thrombosis are two entirely different processes, a population of patients in need of antithrombotic therapy is clearly different from a population of patients in need of inhibition of endothelial cell growth, or in need of anti-angiogenic therapy. Thus, a *primae facie* case of anticipation has not been established for claims 1, 5-6, 57, 60, 63-64, 66, 69-70 and 78, as amended. Moreover, as these processes (thrombosis as compared to endothelial cell growth and angiogenesis) are so radically different, applicants submit that the '097 patent could not possibly be construed to render obvious claims 1, 5-6, 57, 60, 63-64, 66, 69-70 and 78, as amended.

Reconsideration and withdrawal of the rejection are respectfully requested.

Obviousness-Type Double Patenting

Claims 5, 22, and 23 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-9 of United States Patent No. 6,596,690. Applicants strongly disagree with this assertion.

However, solely in the interest of accelerating prosecution, submitted herewith is a terminal disclaimer that disclaims the terminal portion of any patent granted in this application that would extend beyond the expiration date of United States Patent No. 6,596,690.

Applicants submit that the submission of this terminal disclaimer obviates the rejection.

Conclusion

Applicants submit that claims 1, 5, 6, 13-17, 20-25, 57, 60, 63-64, 66, 69-70, 77-81 are in condition for allowance, which action is requested. If any matters remain to be addressed before a Notice of Allowance is issued, the Applicants request that Examiner Yu contact the undersigned for a telephone conference at the telephone number listed below.

Respectfully submitted,

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